INTERNAL MEDICINE

□ CASE REPORT □

Mycobacterium avium Pleuritis in a Non-Immunocompromised Patient

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Abstract

Nontuberculous mycobacterium infection is rarely accompanied by pleural involvement. We describe a very rare occurrence of *Mycobacterium* (*M*) *avium* pleuritis with pleural effusion in a non-compromised 73-year-old woman patient who had been treated for sick sinus syndrome. She was admitted to our hospital with general malaise and left pleural effusion. To establish a definitive diagnosis, a biopsy specimen was obtained from the left parietal pleura by video-assisted thoracoscopic surgery. The pleural biopsy specimen revealed only diffuse lymphoid cell infiltration and neoplastic or granulomatous lesions were absent. Culture of the pleural biopsy specimen revealed *M. avium*, indicating that the pleuritis was caused by this organism. A course of anti-tubercular agents (rifampin, ethambutol and streptomycin sulfate) and clarithromycin gradually resolved the pleural effusion.

Key words: *Mycobacterium avium*, pleuritis, nontuberculous mycobacterium, pleural biopsy

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Introduction

Although the clinical features of infection with nontuberculous mycobacterium (NTM) resemble those of tuberculosis, pleural effusion is rare in cases of NTM infection (1, 2). Signs of infection with *Mycobacterium* (*M*) *avium* begin with centriacinar abnormalities in the lung, with a low incidence of lymphatic abnormalities. Tuberculosis (idiopathic pleuritic type) is thought to cause pleuritis associated with pleural effusion from the primary focus of a pulmonary infection. However, the onset of pleuritis caused by *M. avium* is extremely rare. We describe a non-immunocompromised Japanese woman who developed rare *M. avium* pleuritis.

Case Report

A 73-year-old unemployed Japanese woman was referred to our hospital in January 2007 with general malaise and gradually increasing left pleural effusion. She was a non-smoker who had never been administered with steroids or other immunosuppressants. A permanent pacemaker had been implanted in 1997 to treat sick sinus syndrome. Pleural effusion was not evident on chest X-rays at that time. However, chest X-rays and thoracentesis in 2002 revealed left exudative pleural effusion. Chest computed tomography (CT) also revealed bronchiectasis and small nodules in the right middle lobe and bronchiectasis and partial atelectasis in the left lingular division. Culture and cytological examination of the pleural effusion and a pathological study of pleural needle biopsy materials did not lead to a definitive diagnosis. She remained untreated for 5 years, during which the pleural effusion gradually increased. A physical examination upon admission revealed the following: height, 150 cm tall; weight, 61 kg, arterial blood pressure, 128/76 mmHg; pulse rate, 60/min; temperature, 36.6°C. Respiratory

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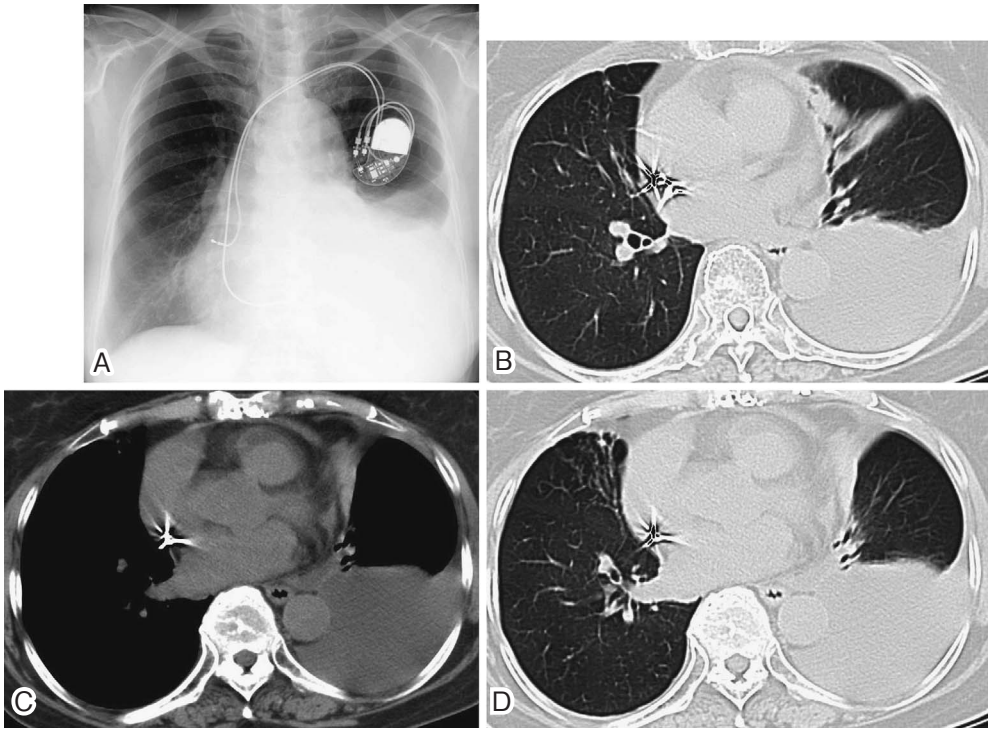

Figure 1. **Chest X-ray (A) and computed tomography (CT) (B) images show massive pleural effusion in the left side. Chest CT also shows bronchiectasis and small nodules in the right middle lobe, as well as bronchiectasis and partial atelectasis in the left lingular division (C and D).**

sound was remarkably diminished on the lower aspects of the left lung. Lymphadenopathy was absent. Laboratory findings revealed the following: white blood cell count, 6,740/mm^3 with 67% neutrophils; elevated C-reactive protein, 2.7 mg/dL (normal range, 0-0.4 mg/dL) and elevated erythrocyte sedimentation, 58 mm/h. A purified protein derivative skin test was obviously positive. Human immunodeficiency virus (HIV) and human T cell lymphotropic virus type I antibodies were negative and malignant complications as well as diabetes mellitus were absent. Chest X-rays and CT scanning revealed pleural effusion in the left lung. Chest CT also revealed bronchiectasis and small nodules in the right middle lobe and bronchiectasis and partial atelectasis in the left lingular division (Fig. 1). This finding was not significantly different from that in 2002. Chest and abdominal CT revealed no lymphadenopathy. Cultures of sputum, bronchial lavage fluid and lung specimens obtained by transbronchial lung biopsy from left S5 were all negative for bacteria, fungi and mycobacteria. The pleural fluid was yellowish and clear. Biochemical analysis of the effusion showed pH 7.5, 4.2 g/dL protein (serum protein 6.2 g/dL), lactate dehydrogenase (LDH) 152 IU/L (serum LDH 214 IU/L), adenosine deaminase 19.5 IU/L and a positive Rivalta reaction. Cytological examination of the effusion showed 88% lymphocytes and no malignant or abnormal cells. Cultures of the pleural effusion were negative for bacteria, fungi and mycobacteria. Polymerase chain reaction (PCR) of the pleural effusion using Amplicor Mycobacterium was negative. Both transbronchial lung and pleural needle biopsies revealed no specific pathological findings such as granuloma formation. To establish a definitive diagnosis, we performed a pleural biopsy from the left parietal pleura by video-assisted thoracoscopic surgery. Macroscopic findings of the visceral and parietal pleura were normal (Fig. 2). The parietal pleural biopsy specimen revealed the band-like, diffuse infiltration of small lymphoid cells in the pleural and subpleural fat without granuloma formation (Fig. 3). No acid-fast positive bacilli were identified. Immunohistochemically, the lymphoid cells consisted of almost equally mixed B-cells and T-cells, so a pathological diagnosis of non-specific lymphocytic pleuritis was made. However, *M. avium* was identified from a culture of the pleural biopsy specimen. No other bacteria was detected. Based on these findings, the final diagnosis was pleuritis due to *M. avium* infection. At the time of thoracoscopic surgery, pleural effusion was drained. However, the pleural effusion increased to the level of admission soon after the surgery. Accordingly, the patient was administered with rifampin 450 mg/day, ethambutol hydrochloride 750 mg/day, clarithromycin 800 mg/day and streptomycin sulfate 900 mg twice weekly, which gradually improved the clinical features. The patient was discharged free of symptoms 3 months after starting the treatment. A chest X-ray at the time of discharge showed that the pleural effusion had decreased (Fig. 4). C-reactive protein and erythrocyte sedimentation gradually decreased to 0.6 mg/dL and 25 mm/h, respectively. She continued the treatment (rifampin 450 mg/day, ethambutol hydrochloride 750 mg/day, clarithromycin 800 mg/day) and attended the outpatient clinic. The pleural effusion continued to gradually decrease, although bronchiectasis and small nodules in the right mid-

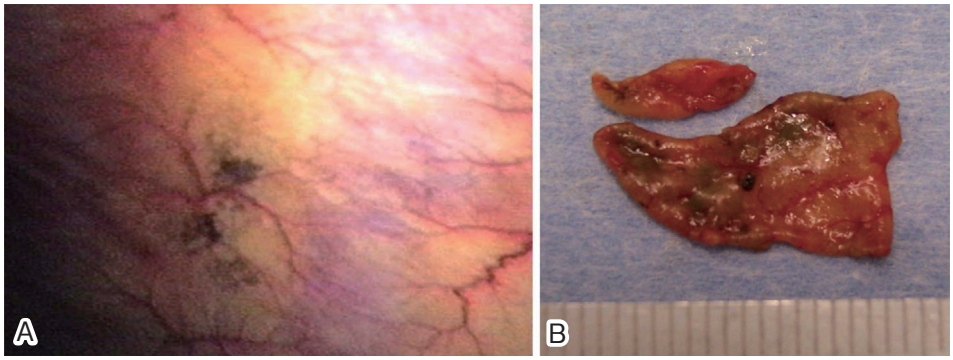

Figure 2. **Macroscopic findings of parietal pleura. Findings are normal. (A) Parietal pleura observed via thoracoscopy. (B) Resected parietal pleura.**

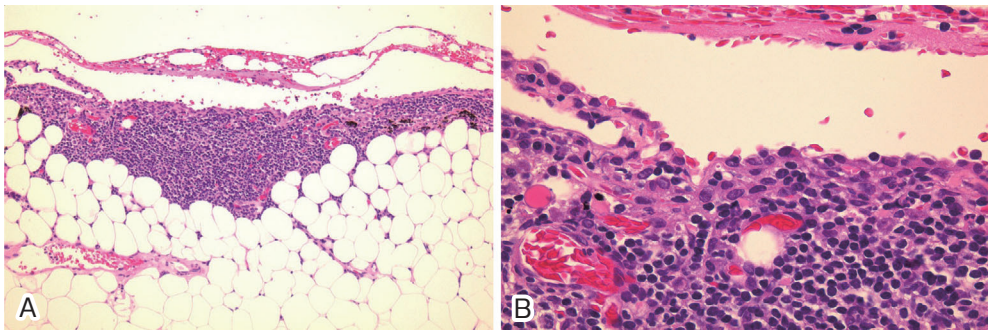

Figure 3. **Parietal pleural biopsy specimen. Band-like, diffuse infiltration of small lymphoid cells in pleural and subpleural fat without granuloma formation.**

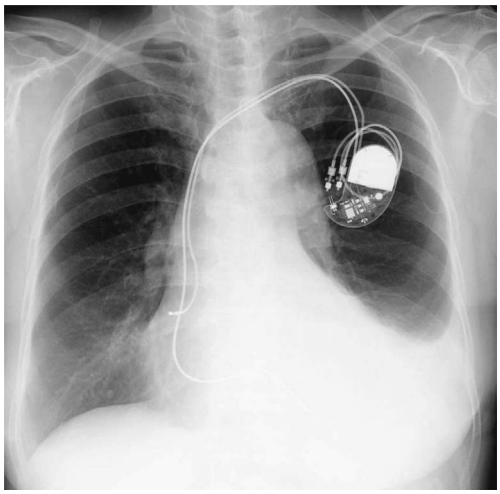

Figure 4. **Chest X-ray at discharge. Pleural effusion was found to have decreased.**

dle lobe and bronchiectasis and partial atelectasis in the left lingular division did not change significantly.

Discussion

The clinical and histological spectrum of pleuropulmonary diseases due to NTM remains obscure and the exact mechanisms of pleuritis onset are unknown. It is possible that NTM may gain entry to a pleural cavity containing an effusion of unrelated etiology through a transient bacteremia or by contiguous spread from a small subpleural focus and may grow in the pleural fluid without eliciting any readily discernible pathologic reaction (3). Accordingly, it is important to make a diagnosis of NTM pleuritis with discretion. In this case, the diagnosis of *M. avium* pleuritis was thought to be appropriate because 1) the other etiology causing exudative pleural effution was excluded, 2) anti-tubercular agents (rifampin, ethambutol and streptomycin sulfate) and clarithromycin were effective, in addition to 3) culture of the pleural biopsy specimen obtained in a sterile fashion revealed *M. avium*. In paticular, thoracoscopic pleural biopsy was thought to be important to exclude the other possible diagnoses.

Nontuberculous mycobacteria might enter the pleural cavity via transient bacteremia and grow in the pleural fluid (3). Transient bacteremia can occur during infection with *M. tuberculosis*, *M. avium intracellulare* (4), and *M. fortuitum-chelonei* (5-7). Pleural involvement without HIV infection has been identified in a patient with disseminated *M. avium-intracellulare* complex infection (8). However, primary NTM pleuritis without disseminated infection is extremely rare. Bacteremia via pacemaker infection was considered for our patient, but, the onset of pleuritis was about 5 years after pacemaker implantation and the patient showed no symptoms or signs of bacteremia, making this scenario unlikely. Another possibility is that *M. avium* could have directly spread from a small subpleural focus to the pleural cavity (3). Chest CT of our patient revealed bronchiectasis and

small nodules in the right middle lobe and left lingular division, suggesting *M. avium* pulmonary infection, so it is possible that direct extension of the pulmonary infection into the pleural space was the cause of the pleural effusion in our case. However, cultured bronchial lavage fluid and lung specimens were negative for mycobacteria. Thoracoscopic visceral pleural and lung biopsy in left lingular division should have been performed to clarify it.

The macroscopic findings of the parietal and visceral pleura were normal and a granulomatous reaction was absent in a pleural biopsy specimen. To our knowledge, this is the first report of macroscopic findings of the pleura obtained via thoracoscopy in *M. avium* pleuritis. In tuberculous pleuritis, granulomatous inflammation can be identified in pleural biopsy specimens in about 60% to 90% of patients (9, 10), which causes macroscopic diffuse white spotted lesion of the pleura. In contrast, an absent granulomatous reaction is often associated with NTM infections (11-13). Patients with AIDS can have disseminated *M. avium* infection with significant numbers of mycobacteria and no granulomatous reaction (14). Others have indicated that malnutrition, impaired cellular immunity, disrupted microvascular circulation due to diabetes mellitus (15, 16) and surgical procedures (17) can enhance the development of pleuritis in infections caused by NTM. Pleuritis caused by NTM in a non-immunocompromised patient is very rare (18, 19). The low virulence of these organisms or immune suppression due to underlying diseases, medication, or both might be responsible for the absence of the typical granulomatous reaction. However, the present patient showed no clinical features or laboratory test results indicating a dysfunctional immune system. The exact mechanisms for the absence of a granulomatous reaction in pleuritis caused by NTM remain unknown.

The incidence of positive cultures arising from pleural fluid is surprisingly low, at only 15% of patients with proven tuberculous pleuritis, whereas cultures of biopsy specimens are positive in 55% to 80% of such patients (20, 21). In the previous reports of *M. avium* pleuritis, culture or PCR method of pleural effusion detected *M. avium* (15, 17-19). However, in this case, culture and PCR of pleural effusion to detect *M. avium* was negative and only the culture of the pleural biopsy specimen revealed *M. avium*. The exact positive ratio of cultured pleural effusions from patients with NTM pleuritis is unknown. However, we postulate that pleural biopsy specimens should be cultured to arrive at a definitive diagnosis. NTM pleuritis might not be so rare, because we previously reported another case of *M. avium* pleuritis in the same institution (19). Diagnostic thoracoscopy is indicated where less invasive investigations do not achieve a clear diagnosis. The proportion of so-called “idiopathic” effusions can be reduced significantly after thoracoscopy. The authors suggest that patients with idiopathic pleural effusion undergo early thoracoscopic pleural biopsy.

In conclusion, physicians should be aware that pleuritis can be caused by NTM and it is recommended to culture both pleural biopsy specimens and effusion when patients present with pleuritis of unknown etiology, even when they are non-immunocompromised and granulomatous reaction is absent in pleural tissues.

References

1. Christensen EE, Dietz GW, Ahn CH, et al. Pulmonary manifestations of *Mycobacterium intracellularis*. AJR Am J Roentgenol **133**: 59-66, 1979.
2. Christensen EE, Dietz GW, Ahn CH, et al. Initial roentgenographic manifestations of pulmonary *Mycobacterium tuberculosis, M. kansasii*, and *M. intracellularis* infections. Chest **80**: 132-136, 1981.
3. Gribetz AR, Damsker B, Marchevsky A, Bottone EJ. Nontuberculous mycobacteria in pleural fluid. Assessment of clinical significance. Chest **87**: 495-498, 1985.
4. Macher AM, Kovacs JA, Gill V, Roberts GD, et al. Bacteremia due to *Mycobacterium avium-intracellulare* in the acquired immunodeficiency syndrome. Ann Intern Med **99**: 782-785, 1983.
5. Geraci JE, Anderson M, Karlson AG. Endocarditis due to a rapidly growing chromogenic mycobacterium. Mayo Clin Proc **43**: 124-133, 1968.
6. Repath F, Seabury JH, Sanders CV, Domer J. Prosthetic valve endocarditis due to *Mycobacterium chelonei*. South Med J **69**: 1244-1246, 1976.
7. Speert DP, Munson D, Mitchell C, et al. *Mycobacterium chelonei* septicemia in a premature infant. J Pediatr **96**: 681-683, 1980.
8. Gotoh T, Fujii T, Hiramori N, et al. [a case of disseminated atypical mycobacteriosis with multiple bronchial polyps]. Nihon Kyobu Shikkan Gakkai Zasshi **28**: 1628-1634, 1990 (in Japanese).
9. Scerbo J, Keltz H, Stone DJ. A prospective study of closed pleural biopsies. JAMA **218**: 377-380, 1971.
10. Kirsch CM, Kroe DM, Azzi RL, Jensen WA, Kagawa FT, Wehner JH. The optimal number of pleural biopsy specimens for a diagnosis of tuberculous pleurisy. Chest **112**: 702-706, 1997.
11. Corpe RF, Stergus I. Is the histopathology of nonphotochromogenic mycobacterial infections distinguishable from that caused by *Mycobacterium tuberculosis*? Am Rev Respir Dis **87**: 289-291, 1963.
12. Kozinn WP, Damsker B, Bottone EJ. *Mycobacterium avium* complex: Significance of isolation from bone marrow culture. J Clin Microbiol **11**: 245-248, 1980.
13. Marchevsky A, Damsker B, Gribetz A, Tepper S, Geller SA. The spectrum of pathology of nontuberculous mycobacterial infections in open-lung biopsy specimens. Am J Clin Pathol **78**: 695-700, 1982.
14. Greene JB, Sidhu GS, Lewin S, et al. *Mycobacterium avium-intracellulare*: A cause of disseminated life-threatening infection in homosexuals and drug abusers. Ann Intern Med **97**: 539-546, 1982.
15. Nagaia T, Akiyama M, Mita Y, Tomizawa T, Dobashi K, Mori M. *Mycobacterium avium* complex pleuritis accompanied by diabetes mellitus. Diabetes Res Clin Pract **48**: 99-104, 2000.
16. Hayashi T, Takayama S, Tominaga S, et al. [a case of pyothorax caused by *Mycobacterium avium*]. Nihon Kokyuki Gakkai Zasshi **44**: 117-121, 2006 (in Japanese).
17. Kawamoto H, Yamagata M, Nakashima H, et al. [development of a case of *Mycobacterium avium* complex disease from right pleural effusion]. Nihon Kokyuki Gakkai Zasshi **38**: 706-709, 2000 (in Japanese).

18. Okada Y, Ichinose Y, Yamaguchi K, Kanazawa M, Yamasawa F, Kawashiro T. *Mycobacterium avium-intracellulare* pleuritis with massive pleural effusion. Eur Respir J **8**: 1428-1429, 1995.
19. Yanagihara K, Tomono K, Sawai T, et al. *Mycobacterium avium* complex pleuritis. Respiration **69**: 547-549, 2002.
20. Klockars M, Petterson T, Riska H, Hellstrom PE. Pleural fluid lysozyme in tuberculous and non-tuberculous pleurisy. Br Med J **1**: 1381, 1976.
21. Levine H, Metzger W, Lacera D, Kay L. Diagnosis of tuberculous pleurisy by culture of pleural biopsy specimen. Arch Intern Med **126**: 269-271, 1970.